

Applicants: Jingrong Cao et al.  
Application No.: 10/696,862

## REMARKS

### The Response

#### *Rejection under 35 U.S.C. § 103(a)*

The Examiner has rejected claims 1, 4, 5, 8-12, 14- 20, 23-29, 31, 33-46, and 54-57 under 35 U.S.C. § 103(a) for allegedly being obvious in view of Inaba et al., Japanese Patent Application No. 2002053566 (hereafter, "Inaba"). In particular, the Examiner asserts that the compounds of Inaba are kinase inhibitors useful for the treatment of Alzheimer's disease and allergy, and that some of the compounds of Inaba are positional isomers of the compounds of the present invention, therefore making the compounds of the present invention not patentably distinct. Applicants traverse.

As in the November 1, 2007 Office Action ("the November Office Action"), the Examiner asserts that Inaba describes compounds that are useful for the treatment of Alzheimer's and allergy. In responding to the November Office Action, applicants stated that they were unable to find the relevant descriptive text in Inaba that relates to the treatment of these diseases by the compounds described therein. Although the Examiner has kindly provided a Japanese-to-English machine translation of the entire reference, he has failed to point to that part of the document that he has relied on for his rejection. The Examiner only cites the sections of Inaba that relate to the description of the compounds of the Inaba invention (i.e., the generic formula found on page 1 and the compound table found on pages 23-99). In particular, the Examiner singles out Inaba compounds 51 and 80 and states that there is no proviso in claim 54 to exclude these compounds. This statement is incorrect because claim 54 is dependent on claim 1, which disclaims compounds 51 and 80.

Furthermore, a fair reading of the translated version of Inaba indicates that this reference does not teach the compounds described therein for the treatment of various diseases, including Alzheimer's disease and allergy. Found in the background section of

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Inaba is the supposition that ten or more isoforms of PKC kinase exist and that one or more these isoforms are involved in a multitude signal transduction pathways of biological significance. See paragraph [0002] of Inaba. The background section then speculates that drugs which check PKC activity may be useful for treating a plethora of diseases, including complications from diabetes, atherosclerosis, inflammatory disorders, disorders of the immune system, central nervous system diseases, and cancer. See paragraph [0003] of Inaba. However, Inaba does not teach what type of PKC inhibitor would be useful for treating any of these diseases or disorders. Instead, Inaba teaches compounds that selectively inhibit PKC-gamma for the treatment of pain. See the translated version of paragraph [0011], which states: “[w]ithout [inhibiting] normal intracellular signal transduction, [an agent that selectively inhibits PKCgamma produces] safe drugs in which remarkable side effects are not shown [and can] especially turn into therapies [for the treatment of pain-related indications].” See also paragraph [0012] of the translated version of Inaba, which states: “[the inventors] came to complete this invention ... in order to find ... a compound which has high PKC inhibitory action and [selectively inhibits] PKC-gamma.” As previously stated in the Reply to the November Office Action that was filed on November 29, 2007, the only biological data presented in Inaba show the *in vitro* inhibition of three PKC isoforms by the compounds exemplified therein or their efficacy in an *in vivo* pain model. See pages 100-112 of Inaba. Since Inaba does not teach the use of the compounds described therein for the treatment of glaucoma, Alzheimer’s disease, an allergy, asthma, or diabetes and since the compounds of the present invention are not described or claimed as sedatives or as PKC inhibitors, there is no nexus that relates the biological activity of the compounds of Inaba to the compounds of the present invention.

The Examiner also asserts that the compounds of Inaba are closely related positional isomers of the compounds of the present invention and that it would have been obvious to one skilled in the art at the time the invention was made to expect the

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compounds of the present invention to possess the utility taught by the compounds of Inaba. However, of the 306 compounds that are exemplified in Inaba, only 7 (compounds 44, 46, 51, 80, 82, 113, and 114) have a pyridyl substituent at the position that corresponds to the pyridin-4-yl substituent of the compounds of the present invention. Biological data are proffered for only 2 of these 7 compounds (compounds 44 and 113) and the PKC inhibition demonstrated for each of these two compounds is less than that of the majority of the other compounds of Inaba for which similar data are reported. For example, of the 246 compounds for which PKC IC<sub>50</sub> data are reported, 222 compounds have activity that is more potent than compound 44 against any one of the tested isoforms (PKC- $\alpha$ , PKC- $\beta$ II, and PKC- $\gamma$ ). The Manual of Patent Examination Procedure (MPEP) states that “[h]omology and isomerism involve close structural similarity which must be considered with all other relevant facts in determining the issue of obviousness” and that these factors “should not be automatically equated with *prima facie* obviousness because the claimed invention and the prior art must each be viewed ‘as a whole.’” See MPEP § 2144.09 (II). See also MPEP § 2141.02, which states that “[a]scertaining the differences between the prior art and the claims at issue requires interpreting the claim language, and considering both the invention and the prior art references as a whole” (emphasis added). The specific compounds of Inaba that were cited by the Examiner in his obviousness rejection represent a small sub-genus of the compounds described therein and are not reflective of the Inaba reference as a whole. Furthermore, the biological activity provided by Inaba for the cited compounds indicate that these compounds are inferior kinase inhibitors compared to the majority of the other compounds described by Inaba, thus teaching away from the preparation or use of pyridinyl thiazoles as kinase inhibitors.

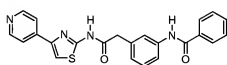
As shown above, there is no nexus that relates the biological activity of the compounds of Inaba to the compounds of the present invention. Further, the vast majority of the compounds exemplified by Inaba (300 out of 307) do not contain a

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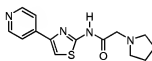
pyridyl substituent that corresponds to the 4-pyridyl substituent of the compounds of the present invention. Further still, the biological activities reported for those Inaba compounds that contain such a pyridyl substituent are inferior to Inaba compounds that do not contain such a substituent. Therefore, nothing in Inaba provides a reason for a person skilled in the art to prepare the pyridine-4-yl compounds of the present invention. Accordingly, applicants respectfully request that the Examiner withdraw the rejections of claims 1, 4, 5, 8-12, 14- 20, 23-29, 31, 33-46, and 54-57 under 35 U.S.C. § 103(a).

#### Information Disclosure Statement

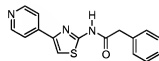
The Examiner has urged applicants to provide references for the disclaimed compounds. The person who drafted the instant application has left the company. In the absence of any notes identifying sources for disclaimed compounds, a structure-based search was performed for the following seven disclaimed compounds of claim 1:



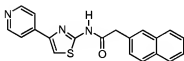
[R<sup>3</sup> is not CH<sub>2</sub>(3-NHCOPh-phenyl)]  
search compound 1



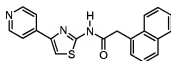
[R<sup>3</sup> is not CH<sub>2</sub>-pyrrolidine]  
search compound 2



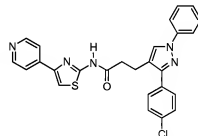
[R<sup>3</sup> is not unsubstituted benzyl]  
search compound 3



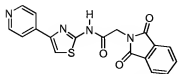
[R<sup>3</sup> is not unsubstituted naphthyl]  
search compound 4



[R<sup>3</sup> is not unsubstituted naphthyl]  
search compound 5



[R<sup>3</sup> is not CH<sub>2</sub>CH<sub>2</sub>-3-(4-Cl-phenyl)-  
1-phenyl-1H-pyrazol-4-yl]  
search compound 6



[R<sup>3</sup> is not CH<sub>2</sub>(1,3-dioxoisindole)]  
search compound 7

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The results of the search indicated that compounds 1 and 3 are described in Inaba as individual compounds (Inaba compound numbers 51 and 80, respectively), compound 2 is generically described in Inaba, and compounds 4-7 have not been described in any document other than the international PCT application that corresponds to the instant application.

#### Conclusion

Applicants request that the Examiner consider the accompanying arguments presented above and allow the claims to pass to issue. Should the Examiner deem expedient a telephone discussion to further the prosecution of the above application, applicants request that the undersigned be contacted at the Examiner's convenience.

Respectfully submitted,

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